



Promoting Responsible Sun Care and Sun Burn Prevention.

State of Montana Professional Indoor Tanning Industry Statistics

Total Number of Professional Indoor Tanning Facility Businesses	160
Total Employment at Professional Tanning Facilities	584
Total Professional Indoor Tanning Facility Customer Base	100,000
Total Economic Impact of Professional Indoor Tanning Facilities	\$18 million

Ownership: The majority of indoor tanning facilities have female ownership, as compared to 26.1 percent of businesses in all industries.

The Professional Indoor Tanning Industry's Position on UV Light

OUR BASE BELIEF: Moderate tanning, for individuals who can develop a tan, is the smartest way to maximize the potential benefits of sun exposure while minimizing the potential risks associated with either too much or too little sunlight.

TANNING'S GOLDEN RULE: Don't ever sunburn. The risks associated with ultraviolet light from the sun and from indoor tanning units are easily managed when consumers avoid sunburn. And indoor tanners are less likely to sunburn outdoors than non-tanners.

PART OF THE SOLUTION: The professional indoor tanning salon industry is part of the solution in the ongoing battle against sunburn and in teaching people how to identify a proper and practical life-long skin care regimen. Indoor tanners are up to 81 percent less likely to sunburn outdoors than non-tanners.

WHO IS BURNING? Sunburn incidence outdoors is increasing in the general population, according to the American Academy of Dermatology. It is *decreasing* among indoor tanners.

BENEFITS: Human life is totally reliant on sun exposure, and the life-giving effects of ultraviolet light. The anti-tanning lobby has failed to recognize that people derive any benefit from UV exposure. There are known physiological and psychological benefits associated with sun exposure. There are many other potential benefits that need further research.

TANNING IS NATURAL: Humans need ultraviolet light exposure to survive. Without it, we would be unable to synthesize many chemicals our bodies need. A tan is the body's natural protection against sunburn. Your skin is designed to tan as a regular body function, and the body is designed to repair sun damage as a natural process. For that reason, it is inaccurate to call tanning "damage" to the skin. It is natural and is what the body is intended to do.

Sources for Economic Data: International Smart Tan Network survey of indoor tanning facility customer bases. United States Census data. This document created for the Indoor Tanning Association by the International Smart Tan Network. Do not reproduce this document without the expressed permission of the International Smart Tan Network.

The Indoor Tanning Association is a national trade association representing all major manufacturers, suppliers and distributors of indoor sun tanning equipment as well as professional sun tanning facilities nationwide.

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Regulation of the Indoor Tanning Industry – Indoor tanning facilities in Montana are already strictly regulated by the Food and Drug Administration under (21 CFR 1040.20). The regulations require visible warning signs, use of eyewear, maximum timer intervals specified by regulation and instructions to users to avoid or minimize injury. There are strict limits on the output of the equipment.

In addition, the FDA has spent a great deal of time and energy determining maximum exposure times thus making indoor tanning far less potentially harmful than exposure to the summer sun. The FDA also requires a warning sign on each device that must be clearly legible by the customer.

That sign reads as follows:

"DANGER Ultraviolet radiation. Follow instructions. Avoid overexposure. As with natural sunlight, overexposure can cause eye and skin injury and allergic reactions. Repeated exposure may cause premature aging of the skin and skin cancer. WEAR PROTECTIVE EYEWEAR; FAILURE TO MAY RESULT IN SEVERE BURNS OR LONG-TERM INJURY TO THE EYES. Medications or cosmetics may increase your sensitivity to the ultraviolet radiation. Consult physician before using sunlamp if you are using medications or have a history of skin problems or believe yourself especially sensitive to sunlight. If you do not tan in the sun, you are unlikely to tan from use of this product."

Review of the complaints/injuries reported to the FDA in the years of 1993-2006 found a total of 49 injuries for the entire United States. During that 14 year period, there were an estimated 5.1 billion tanning sessions. That reflects an injury incidence rate of .000001%, or one reported injury per 100 million tanning sessions; an industry safety record of which we are proud.

Over the past 20 years the same special interest groups who are attacking our industry have tried unsuccessfully to force the Federal Government to ban this industry or severely restrict how these businesses operate. Under Federal law, the FDA is required to examine the facts and study all sides of the issue. After reviewing the data, the FDA has time and again, come to the same conclusion, there is no merit to these arguments and have allowed tanning salons and the families that run them to continue to operate.

Additional Warning to Customers –In addition to the warning label required by the FDA, “informed consent” forms are also standard practice. When any customer comes to an indoor sun tanning facility, they are warned about the potential dangers of overexposure to ultraviolet light. The warning is conveyed by having each customer read and sign what we call an “informed consent” form. Most insurance carriers for tanning salons require the use of such a form. Further, giving clients an honest assessment of the potential benefits and risks associated with UV light exposure is the right thing to do. These forms play a key role in informing the customer about photo-sensitive drugs; the need for protective eyewear and confirm that the customer is 18 years or older. When the customer is a minor, a parent or guardian must sign.

Parental consent for individuals under age 18 –is a standard practice for businesses in Montana and across the US. If the individual is younger than 18, professional salons require that a consent form be signed by a parent or guardian. If the minor’s parent doesn’t approve, the minor would not be allowed to use the facility

Indoor Sun Tanning Prevents Dangerous Sunburn -- While repeated sunburn may contribute to skin problems later in life, our industry seeks to prevent the risks associated with sunburn. Professional tanning facilities work to manage exposure to ultraviolet light, based on the unique skin characteristics of each client, so that sunburn is avoided. As a result, the incidence of sunburn among those who use indoor tanning facilities is decreasing. Indoor tanners are up to 81 percent less likely to sunburn outdoors than those who do not use indoor tanning.

Benefits of exposure to UV Light – Unfortunately, over the past 25-30 years, the American public has been subjected to one of the most successful public relations campaigns in history, a campaign to keep people out of the sun. Countless millions, possibly hundreds of millions of dollars, have been spent to publicize the risk of exposure and therefore the benefits of UV exposure have been overshadowed by companies trying profit by the public's alarm.

This seems to be changing and both sides of the story are finally getting out. As more money is devoted to research on the benefits of UV light, all of us stand to gain from these scientific findings and the implications of such research.

The benefit we know most about is Vitamin D. UV light striking your skin is the only way the body produces Vitamin D, a nutrient that is essential for good health.

Many scientists now believe the pendulum has swung way too far to one side on the question of sun exposure. In fact, only last year the National Institute of Health held a day long symposium to discuss what some experts call “an epidemic of Vitamin D deficiency in the United States.”

What we now know the following to be true:

- Ultraviolet light is ultraviolet light, whether from the sun or a sunbed.
- According to Harvard Study, 60% of Americans are vitamin D deficient.
- Vitamin D deficiency is associated with an increased risk of colon, prostate and breast cancer and is shown to ward off heart disease, MS, and other chronic health problems.
- Recent research shows that the benefits associated with vitamin D outweigh any potential risks associated with exposure to UV light.
- Doctors estimate that there are over one billion people worldwide at risk of vitamin D deficiency, with 30-50% of children and adults in the United States at high risk for this dangerous condition.

- Vitamin D is also linked to many common wintertime complaints such as fatigue, depression and aches and pains.
- It is impossible to get the requisite amount of vitamin D in cities north of 37 degrees for as many as 6 months out of the year. That includes all cities north of Atlanta GA.
- Vitamin D isn't like other vitamins that you can easily ingest as part of your diet. It is best absorbed through the skin from exposure to UV light. New research indicates that supplement-based vitamin D, as opposed to vitamin D naturally produced through exposure to UV light, may actually harm the body's ability to fight disease

It is also a fact that the major source of vitamin D (80-100%) for children and adults in the United States comes from exposure to ultraviolet energy. Avoidance of all direct sun exposure places children and adults at high risk of vitamin D deficiency. It is difficult to obtain the necessary 1,000 IU of vitamin D each day to maintain healthy vitamin D levels. Therefore, much of the population in the United States is vitamin D deficient.

Vitamin D deficiency is a dangerous condition in both children and adults. In children, vitamin D deficiency prevents them from attaining their maximum height and bone mineral density (bone health). Vitamin D deficient children also have a drastically increased risk of developing osteoporosis and fractures later in life. In adults, vitamin D deficiency causes osteomalacia, a condition with symptoms including bone pain and muscle weakness. Therefore the maintenance of healthy vitamin D levels acts as a preventative measure against some of the most deadly diseases in the United States.

Epidemiologic studies have been completed showing that as your exposure to Ultraviolet light decreases, your risk of the most common deadly cancers (including prostate, colon, lung, and breast cancers), heart disease, diabetes type I as well as several autoimmune disorders including multiple sclerosis increases.

Cancer experts say the risks posed by other cancers is far greater than that of skin cancer, which is rarely fatal. Melanoma, the deadliest kind, is expected to account for just 1.4 percent of the 570,000 cancer deaths in the United States this year.



Frequently Asked Questions about Indoor Tanning and Health ***Let Moderate Exposure to UV Light Shine In***

Is moderate exposure to the sun or ultraviolet (UV) light good for your health?

Absolutely. There is a mountain of well conducted, validated science that demonstrates that the production of the activated form of vitamin D is one of the most effective ways the body controls abnormal cell growth. Moderate exposure to sunlight is the only way for the body manufacture the vitamin D which is necessary for the body to produce activated vitamin D.

How much vitamin D do you need?

A 1997 report by the National Academy of Sciences Institute of Medicine recommends 200 IU/day of vitamin D for women aged 50 years or younger, 400 IU/day for those aged 51-70 and 600 IU/day for those older than 70 years.¹ In fact, leading experts in the field believe these recommendations are totally inadequate to protect public health. There is no question that the country faces a severe vitamin D deficiency epidemic. New science strongly supports changing the current recommendation to 1000 IU/day for adults.

What is the best way to help the body produce the activated form of vitamin D?

Moderate exposure to sunlight is the only way to help the body manufacture the vitamin D it needs. While eating salmon or mackerel and drinking fortified milk or juices is a step in the right direction, it is practically impossible to consume enough of these products every day to meet dietary needs. For example, one would have to consume ten glasses a day of fortified juices or milk every day of the year to meet nutritional requirements.

How does the skin make vitamin D and what limits its production?

Sun or UV light is the fuel that permits to body to manufacture vitamin D. But the amount of vitamin D formed in a given period of exposure depends on the color of your skin -- that is, how rich the skin is in melanin. Melanin absorbs UV radiation therefore it diminishes the production of vitamin D.

The darker a person's skin, the longer he or she has to be in sun or exposed to UVB radiation to form a significant amount of vitamin D.² Like melanin, sunscreen also absorbs UV radiation and therefore greatly diminishes vitamin D production by the skin.

For example, a sunscreen with a SPF of 8 diminishes ability to produce vitamin D by 95%. In addition, winter sunlight in the northern latitudes (New York City, Boston, and San Francisco) does not have enough UVB radiation to produce vitamin D in the skin. This is the reason most Americans are at risk for vitamin D deficiency, especially in the winter. A national study showed that 42% of African-American women ages 15 to 49 were deficient in vitamin D by the end of winter.³ In addition, a recent study of young Caucasian women ages 9-11 in Maine found 48% were vitamin D deficient at the end of the winter.

When do people get most of their exposure to UV light?

Most people receive the highest percentage of their lifetime exposure to UV light after the age of 40. People receive less than 25% of their lifetime dose by the age of 18.

Is, moderate exposure to UVB radiation associated with decreased rates of cancer and other disease?

Yes. In fact, the inaugural edition of *The Journal of Cancer* in 1941 reported that the increased risk of non-melanoma cancer was a price to be paid for a decrease in internal cancer.

According to the nation's leading expert in the field, Dr. Michael F. Holick, a professor of medicine, dermatology, physiology and biophysics at the Boston University School of Medicine, relatively brief exposure to sunshine or its equivalent several times a week in tanning beds can help to ward off a host of debilitating and sometimes deadly diseases, including osteoporosis, hypertension, diabetes, depression,⁴ and cancer of the bladder, breast, colon, ovary, uterus, kidney, and prostate, as well as multiple myeloma and non-Hodgkin's lymphoma.⁵

How do the "risks and benefits" of, moderate UV radiation exposure net out?

The protective benefits of UV radiation are undeniable. Warnings about limited and sensible exposure to the sun or UV radiation are greatly exaggerated.

Several researchers, most notably Dr. William Grant have published peer-reviewed articles that demonstrate, that in America, for example, increased sun exposure would result in 185,000 fewer cases of internal cancer and 30,000 fewer deaths from cancer of the breast, ovaries, colon, prostate, bladder, uterus, esophagus, rectum and stomach.⁶ By comparison, about 7500 die each year from skin cancer. UV exposure also protects against the development of multiple sclerosis, a devastating autoimmune disease. During adolescence, higher sun exposure (average 2-3 hours or more a day in summer during weekends and holidays) is associated with a 69% decreased risk of developing multiple sclerosis.⁷ Similar protective benefits of sun exposure and/or increase in the intake of vitamin D have been reported with other autoimmune diseases like rheumatoid arthritis and Type 1 diabetes, which is usually diagnosed in children and young adults. In

addition, studies have show that sun exposure and/or increase in the intake of vitamin D can delay of onset of prostate cancer 3-5 years.

What is moderate exposure?

Moderate exposure is the most responsible way to maximize the potential benefits of sun or UV exposure while minimizing the potential risks associated with either too much or too little sunlight. Avoiding sunburns is a critical to moderation. Painful sunburns before the age of 20, not lifetime sun exposure, is associated with an increased risk of malignant melanoma, the most serious type of skin cancer.⁸

According to Holick, optimal sunlight exposure time—and, in turn, optimal vitamin D production—will vary according to skin color, location, and time of year. African-American, Hispanics and people with a Mediterranean heritage require more. Blue-eyed, red heads from northern Europe need far less. The one basic rule that applies to everyone is avoiding sun burn. It is the burning of the skin and chronic excessive exposures, not the limited sensible exposure to ultraviolet light or sunlight, that creates the concern about skin cancer.

How does the medical community characterize skin types?

According to the American Academy of Dermatology there are six skin types:⁹

Skin Type	Sunburn and Tanning History	Example
I.	Always burns; never tans	Pale white skin; "Celtic"
II.	Burns easily; tans minimally	White skin
III.	Burns moderately; tans gradually to light brown	Average Caucasian skin
IV.	Burns minimally; always tans well to moderately brown	Olive skin
V.	Rarely burns; tans profusely to dark	Brown skin
VI.	Never burns; deeply pigmented	Black skin

What should people do to prevent burning after they receive a moderate exposure to UV light?

The best advice is to cover up or apply a generous amount (about 1 ounce) of a broad spectrum sunscreen that blocks both UVA and UVB rays at least once every four hours.

What are the risks of overexposure to UV radiation?

Overexposure to UV radiation, particularly when it results in burns, may cause skin cancer. Overexposure to UV radiation can also have a damaging effect on the immune

system and cause premature aging of the skin, giving it a wrinkled, leathery appearance. About 1 million new skin cancer cases are likely to be diagnosed in the U.S. this year.¹⁰

What is melanoma?

Melanoma is a cancer of the pigment producing cells (melanocytes). There has been an association with increase risk of melanoma if you have moles or repeated sunburn experiences as a child or young adult. Most melanomas occur on non-sun exposed parts of the body. For example, melanoma is infrequently found on the face.

Although melanoma accounts for only 5% of all newly diagnosed skin cancer cases each year, it is responsible for the majority of skin cancer deaths.¹¹

Is melanoma associated with UV exposure from tanning beds?

No. To date, no well-designed studies support the connection between melanoma and UV exposure from tanning beds.¹²

The relationship between melanoma and UV light exposure is complex. For example, melanoma is more common in people who work indoors than in those who work outdoors, and those who work both indoors and outdoors develop the fewest melanomas.¹³ Further, melanoma most commonly appears on parts of the body that do not receive regular exposure to UV light.¹³

Who regulates the indoor tanning industry?

The FDA provides extensive regulation of the indoor tanning industry. FDA regulations require each device to bear detailed consumer information to avoid over exposure. The label displays a recommended exposure schedule for skin types II-V. The label warns that certain medications or cosmetics may increase sensitivity to UV light. Those regulations can be found at 21CFR 1040.20.

¹ Malabanan AO, Holick MF. vitamin D and bone health in postmenopausal women. *J Womens Health* (Larchmt). 2003 Mar;12(2):151-6.

² Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet*. 1982 Jan 9;1(8263):74-6.

³ Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr*. 2002 Jul;76(1):187-92.

⁴ Brody, J. A Second Opinion on Sunshine: It Can Be Good Medicine After All. *The New York Times*. June 17, 2003.

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- ⁵ Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. *Recent Results Cancer Res.* 2003;164:371-7.
- ⁶ Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer.* 2002 Mar 15;94(6):1867-75.
- ⁷ van der Mei IA, Ponsonby AL, Dwyer T, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ.* 2003 Aug 9;327(7410):316.
- ⁸ Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN; Leiden Skin Cancer Study. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol.* 2003 Jun;120(6):1087-93.
- ⁹ American Academy of Dermatology website. www.aad.org/ Accessed July 28, 2003.
- ¹⁰ National Cancer Institute website, www.cancer.gov/cancerinfo/ Accessed July 30, 2003.
- ¹¹ American Cancer Society. Skin Cancer: Melanoma. Available online at: http://www.cancer.org/docroot/CRI/CRI_2_1x.asp?dt=39. Accessed August 13, 2003.
- ¹² Swerdlow AJ, Weinstock MA. Do tanning lamps cause melanoma? An epidemiologic assessment. *J Am Acad Dermatol.* 1998 Jan;38(1):89-98.
- ¹³ Garland FC, White MR, Garland CF, Shaw E, Gorham ED. Occupational sunlight exposure and melanoma in the U.S. Navy. *Arch Environ Health.* 1990 Sep-Oct;45(5):261-7.

REVIEW ARTICLE

MEDICAL PROGRESS

Vitamin D Deficiency

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N Engl J Med 2007;357:266-81.

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ONCE FOODS WERE FORTIFIED WITH VITAMIN D AND RICKETS APPEARED to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D–deficiency iceberg. In fact, vitamin D deficiency remains common in children and adults. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture.

The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease. In this review I consider the nature of vitamin D deficiency, discuss its role in skeletal and nonskeletal health, and suggest strategies for its prevention and treatment.

SOURCES AND METABOLISM OF VITAMIN D

Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements.¹⁻⁴ A diet high in oily fish prevents vitamin D deficiency.³ Solar ultraviolet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D₃, which is rapidly converted to vitamin D₃ (Fig. 1).¹ Because any excess previtamin D₃ or vitamin D₃ is destroyed by sunlight (Fig. 1), excessive exposure to sunlight does not cause vitamin D₃ intoxication.²

Few foods naturally contain or are fortified with vitamin D. The “D” represents D₂ or D₃ (Fig. 1). Vitamin D₂ is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D₃ through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used in over-the-counter vitamin D supplements, but the form available by prescription in the United States is vitamin D₂.

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (Fig. 1), which is used to determine a patient's vitamin D status¹⁻⁴; 25-hydroxyvitamin D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D.¹⁻⁴ The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels.¹⁻⁴ Fibroblast growth factor 23, secreted from the bone, causes the sodium–phosphate cotransporter to be internalized by the cells of the kidney and small intestine and also suppresses 1,25-dihydroxyvitamin D synthesis.⁵ The efficiency of the absorption of renal calcium and of intestinal calcium and phosphorus is increased in the presence of 1,25-dihy-

droxyvitamin D (Fig. 1).^{2,3,6} It also induces the expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24), which catabolizes both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D into biologically inactive, water-soluble calcitroic acid.²⁻⁴

DEFINITION AND PREVALENCE OF VITAMIN D DEFICIENCY

Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter).⁷⁻¹⁰ 25-Hydroxyvitamin D levels are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng per milliliter (75 to 100 nmol per liter), at which point parathyroid hormone levels begin to level off (at their nadir).¹⁰⁻¹² Furthermore, intestinal calcium transport increased by 45 to 65% in women when 25-hydroxyvitamin D levels were increased from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter).¹³ Given such data, a level of 25-hydroxyvitamin D of 21 to 29 ng per milliliter (52 to 72 nmol per liter) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng per milliliter or greater can be considered to indicate sufficient vitamin D.¹⁴ Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng per milliliter (374 nmol per liter).

With the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.^{7-12,15-22} According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D.^{7-12,15-22} More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-hydroxyvitamin D — below 30 ng per milliliter (75 nmol per liter).^{12,22}

Children and young adults are also potentially at high risk for vitamin D deficiency. For example, 52% of Hispanic and black adolescents in a study in Boston²³ and 48% of white preadolescent girls in a study in Maine²⁴ had 25-hydroxyvitamin D levels below 20 ng per milliliter. In other studies, at the end of the winter, 42% of 15- to 49-year-old black girls and women throughout the United States had 25-hydroxyvitamin D levels below 20 ng per milliliter,²⁵ and 32% of healthy students, phy-

sicians, and residents at a Boston hospital were found to be vitamin D-deficient, despite drinking a glass of milk and taking a multivitamin daily and eating salmon at least once a week.²⁶

In Europe, where very few foods are fortified with vitamin D, children and adults would appear to be at especially high risk.^{1,7,11,16-22} People living near the equator who are exposed to sunlight without sun protection have robust levels of 25-hydroxyvitamin D — above 30 ng per milliliter.^{27,28} However, even in the sunniest areas, vitamin D deficiency is common when most of the skin is shielded from the sun. In studies in Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 20 ng per milliliter.²⁹⁻³² Also at risk were pregnant and lactating women who were thought to be immune to vitamin D deficiency since they took a daily prenatal multivitamin containing 400 IU of vitamin D (70% took a prenatal vitamin, 90% ate fish, and 93% drank approximately 2.3 glasses of milk per day)³³⁻³⁵; 73% of the women and 80% of their infants were vitamin D-deficient (25-hydroxyvitamin D level, <20 ng per milliliter) at the time of birth.³⁴

CALCIUM, PHOSPHORUS, AND BONE METABOLISM

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed.²⁻⁴ The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80% (Fig. 1).^{2-4,13}

In one study, serum levels of 25-hydroxyvitamin D were directly related to bone mineral density in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng per milliliter or more.⁸ When the level was 30 ng per milliliter or less, there was a significant decrease in intestinal calcium absorption¹³ that was associated with increased parathyroid hormone.¹⁰⁻¹² Parathyroid hormone enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D.^{2-4,6} Parathyroid hormone also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts (Fig. 1).¹⁻³ Osteoclasts dissolve the mineralized collagen matrix in bone, causing os-

teopenia and osteoporosis and increasing the risk of fracture.^{7,8,11,16-21}

Deficiencies of calcium and vitamin D in utero and in childhood may prevent the maximum deposition of calcium in the skeleton.³⁶ As vitamin D deficiency progresses, the parathyroid glands are maximally stimulated, causing secondary hyperparathyroidism.^{7,9-12} Hypomagnesemia blunts this response, which means that parathyroid hormone levels are often normal when 25-hydroxyvitamin D levels fall below 20 ng per milliliter.³⁷ Parathyroid hormone increases the metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which further exacerbates the vitamin D deficiency. Parathyroid hormone also causes phosphaturia, resulting in a low-normal or low serum phosphorus level. Without an adequate calcium-phosphorus product (the value for calcium times the value for serum phosphorus), mineralization of the collagen matrix is diminished, leading to classic signs of rickets in children^{1,28} and osteomalacia in adults.^{7,38}

Whereas osteoporosis is unassociated with bone pain, osteomalacia has been associated with isolated or generalized bone pain.^{39,40} The cause is thought to be hydration of the demineralized gelatin matrix beneath the periosteum; the hydrated matrix pushes outward on the periosteum, causing throbbing, aching pain.⁷ Osteomalacia can often be diagnosed by using moderate force to press the thumb on the sternum or anterior tibia, which can elicit bone pain.^{7,40} One study showed that 93% of persons 10 to 65 years of age who were admitted to a hospital emergency department with muscle aches and bone pain and who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D.⁴¹

OSTEOPOROSIS AND FRACTURE

Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis.^{16,20} It is estimated that 47% of women and 22% of men 50 years of age or older will sustain an osteoporotic fracture in their remaining lifetime. Chapuy et al.²¹ reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D₃ daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%. A 58%

Figure 1 (facing page). Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism.

During exposure to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol in the skin is converted to previtamin D₃, which is immediately converted to vitamin D₃ in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D₃ and vitamin D₃ into inactive photoproducts. Vitamin D₂ and vitamin D₃ from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (hereafter "D" represents D₂ or D₃) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D-binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. (Although most laboratories report the normal range to be 20 to 100 ng per milliliter [50 to 250 nmol per liter], the preferred range is 30 to 60 ng per milliliter [75 to 150 nmol per liter].) This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase) to the biologically active form — 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of 1,25(OH)₂D. 1,25(OH)₂D decreases its own synthesis through negative feedback and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. 1,25(OH)₂D increases the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)₂D to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. 1,25(OH)₂D enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor-retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). 1,25(OH)₂D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor- κ B ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate calcium (Ca²⁺) and phosphorus (HPO₄²⁻) levels promote the mineralization of the skeleton.

reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D₃ and 500 mg of calcium per day.⁴²

A meta-analysis of seven randomized clinical

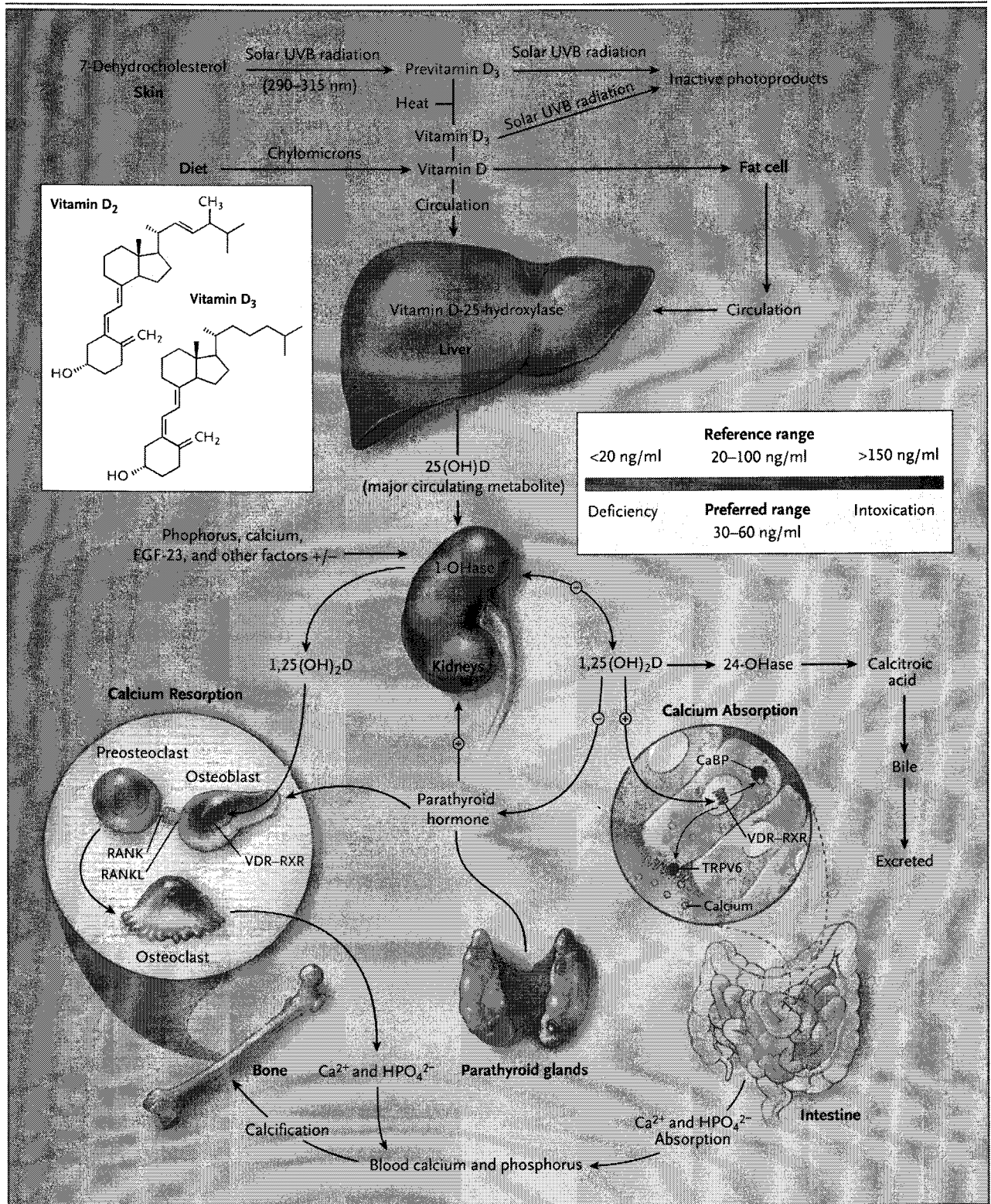


Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D₂ and D₃.*

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D ₃
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D ₃ or D ₂
Canned (3.5 oz)	About 300–600 IU of vitamin D ₃
Sardines, canned (3.5 oz)	About 300 IU of vitamin D ₃
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D ₃
Tuna, canned (3.6 oz)	About 230 IU of vitamin D ₃
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D ₃
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D ₂
Sun-dried (3.5 oz)	About 1600 IU of vitamin D ₂
Egg yolk	About 20 IU of vitamin D ₃ or D ₂
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythral dose)†	About 3000 IU of vitamin D ₃
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D ₃
Fortified orange juice	About 100 IU/8 oz vitamin D ₃
Infant formulas	About 100 IU/8 oz vitamin D ₃
Fortified yogurts	About 100 IU/8 oz, usually vitamin D ₃
Fortified butter	About 50 IU/3.5 oz, usually vitamin D ₃
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D ₃
Fortified cheeses	About 100 IU/3 oz, usually vitamin D ₃
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D ₃
Supplements	
Prescription	
Vitamin D ₂ (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D ₂) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D ₂ , or D ₃ ‡
Vitamin D ₃	400, 800, 1000, and 2000 IU

* IU denotes international unit, which equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.

† About 0.5 minimal erythral dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity) of the arms and legs to direct sunlight.

‡ When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D₂; cholecalciferol or vitamin D₃ indicates that the product contains vitamin D₃.

trials that evaluated the risk of fracture in older persons given 400 IU of vitamin D₃ per day revealed little benefit with respect to the risk of either nonvertebral or hip fractures (pooled relative risk of hip fracture, 1.15; 95% confidence interval [CI], 0.88 to 1.50; pooled relative risk of nonvertebral fracture, 1.03; 95% CI, 0.86 to 1.24). In studies using doses of 700 to 800 IU of vitamin D₃ per day, the relative risk of hip fracture was reduced by 26% (pooled relative risk, 0.74; 95% CI, 0.61 to 0.88), and the relative risk of nonvertebral fracture by 23% (pooled relative risk, 0.77; 95% CI, 0.68 to 0.87) with vitamin D₃ as compared with calcium or placebo.⁸ A Women's Health Initiative study that compared the effects of 400 IU of vitamin D₃ plus 1000 mg of calcium per day with placebo in more than 36,000 postmenopausal women confirmed these results, reporting an increased risk of kidney stones but no benefit with respect to the risk of hip fracture.

The Women's Health Initiative study also showed that serum levels of 25-hydroxyvitamin D had little effect on the risk of fracture when levels were 26 ng per milliliter (65 nmol per liter) or less. However, women who were most consistent in taking calcium and vitamin D₃ had a 29% reduction in hip fracture.⁴³ Optimal prevention of both nonvertebral and hip fracture occurred only in trials providing 700 to 800 IU of vitamin D₃ per day in patients whose baseline concentration of 25-hydroxyvitamin D was less than 17 ng per milliliter (42 nmol per liter) and whose mean concentration of 25-hydroxyvitamin D then rose to approximately 40 ng per milliliter.⁸

Evaluation of the exclusive use of calcium or vitamin D₃ (RECORD trial) showed no antifracture efficacy for patients receiving 800 IU of vitamin D₃ per day.⁴⁴ However, the mean concentration of 25-hydroxyvitamin D increased from 15.2 ng per milliliter to just 24.8 ng per milliliter (37.9 to 61.9 nmol per liter), which was below the threshold thought to provide antifracture efficacy.⁸ Porthouse and colleagues,⁴⁵ who evaluated the effect of 800 IU of vitamin D₃ per day on fracture prevention, did not report concentrations of 25-hydroxyvitamin D. Their study had an open design in which participants could have been ingesting an adequate amount of calcium and vitamin D separate from the intervention. This called into question the conclusion that vitamin D supplementation had no antifracture benefit.⁸

MUSCLE STRENGTH AND FALLS

Vitamin D deficiency causes muscle weakness.^{1,7,8,28} Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function.^{1,8}

Performance speed and proximal muscle strength were markedly improved when 25-hydroxyvitamin D levels increased from 4 to 16 ng per milliliter (10 to 40 nmol per liter) and continued to improve as the levels increased to more than 40 ng per milliliter (100 nmol per liter).⁸ A meta-analysis of five randomized clinical trials (with a total of 1237 subjects) revealed that increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.⁸ The same meta-analysis examined the frequency of falls and suggested that 400 IU of vitamin D₃ per day was not effective in preventing falls, whereas 800 IU of vitamin D₃ per day plus calcium reduced the risk of falls (corrected pooled odds ratio, 0.65; 95% CI, 0.4 to 1.0).⁸ In a randomized controlled trial conducted over a 5-month period, nursing home residents receiving 800 IU of vitamin D₂ per day plus calcium had a 72% reduction in the risk of falls as compared with the placebo group (adjusted rate ratio, 0.28%; 95% CI, 0.11 to 0.75).⁴⁶

NONSKELETAL ACTIONS
OF VITAMIN D

Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D.^{1-4,6} In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1 α -hydroxylase.^{1-3,6}

Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.^{1,2,47} It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation.^{1-3,6,47} One practical application is the use of 1,25-dihydroxyvitamin D₃ and its active analogues for the treatment of psoriasis.^{48,49}

1,25-Dihydroxyvitamin D is also a potent immunomodulator.^{2-4,6,50} Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the vitamin D

receptor gene and the 25-hydroxyvitamin D-1 α -hydroxylase gene. Increased production of 1,25-dihydroxyvitamin D₃ result in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. When serum levels of 25-hydroxyvitamin D fall below 20 ng per milliliter (50 nmol per liter), the monocyte or macrophage is prevented from initiating this innate immune response, which may explain why black Americans, who are often vitamin D-deficient, are more prone to contracting tuberculosis than are whites, and tend to have a more aggressive form of the disease.⁵¹ 1,25-dihydroxyvitamin D₃ inhibits renin synthesis,⁵² increases insulin production,⁵³ and increases myocardial contractility (Fig. 2).⁵⁴

LATITUDE, VITAMIN D DEFICIENCY,
AND CHRONIC DISEASES

CANCER

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes.⁵⁵⁻⁶⁵ Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers.^{56,59-61,64} An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of 25-hydroxyvitamin D (the odds ratio at 16.2 ng per milliliter [40.4 nmol per liter] was 1.0, and the odds ratio at 39.9 ng per milliliter [99.6 nmol per liter] was 0.53; $P \leq 0.01$). Serum 1,25-dihydroxyvitamin D levels were not associated with colorectal cancer.⁶¹ A prospective study of vitamin D intake and the risk of colorectal cancer in 1954 men showed a direct relationship (with a relative risk of 1.0 when vitamin D intake was 6 to 94 IU per day and a relative risk of 0.53 when the intake was 233 to 652 IU per day, $P < 0.05$).⁵⁶ Participants in the Women's Health Initiative who at baseline had a 25-hydroxyvitamin D concentration of less than 12 ng per milliliter (30 nmol per liter) had a 253% increase in the risk of colorectal cancer over a follow-up period of 8 years.⁶² In a study

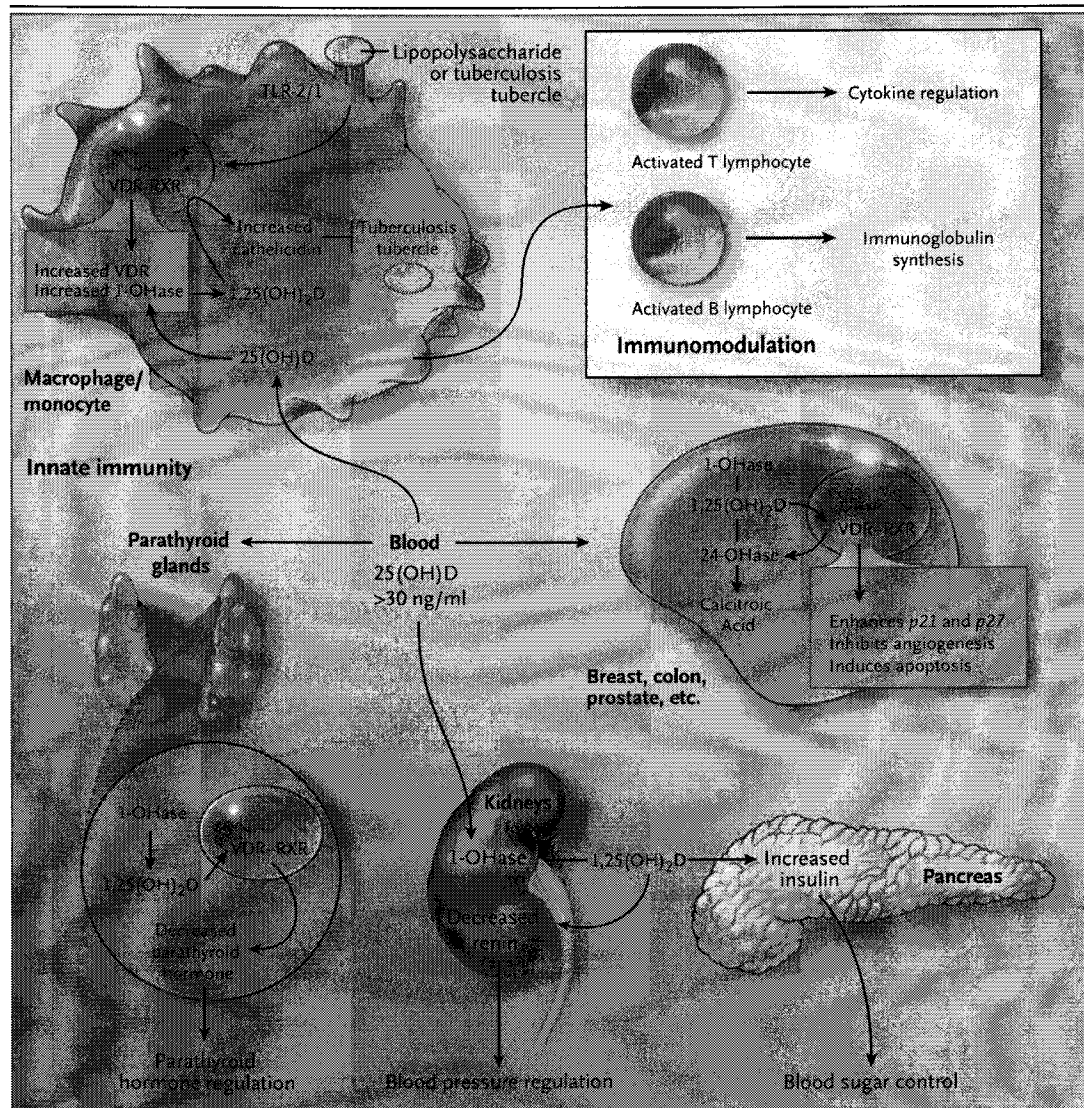


Figure 2. Metabolism of 25-Hydroxyvitamin D to 1,25-Dihydroxyvitamin D for Nonskeletal Functions.

When a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as *Mycobacterium tuberculosis* or its lipopolysaccharide, the signal up-regulates the expression of vitamin D receptor (VDR) and 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase). A 25-hydroxyvitamin D [25(OH)D] level of 30 ng per milliliter (75 nmol per liter) or higher provides adequate substrate for 1-OHase to convert 25(OH)D to its active form, 1,25 dihydroxyvitamin D [1,25(OH)₂D]. 1,25(OH)₂D travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*. It is also likely that the 1,25(OH)₂D produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 30 ng per milliliter, the risk of many common cancers is reduced. It is believed that the local production of 1,25(OH)₂D in the breast, colon, prostate, and other tissues regulates a variety of genes that control proliferation, including p21 and p27, as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once 1,25(OH)₂D completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (24-OHase), which enhances the catabolism of 1,25(OH)₂D to the biologically inert calcitroic acid. Thus, locally produced 1,25(OH)₂D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity, and the local production of 1,25(OH)₂D inhibits the expression and synthesis of parathyroid hormone. The 1,25(OH)₂D produced in the kidney enters the circulation and can down-regulate renin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas.

of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors.⁶³ Pooled data for 980 women showed that the highest vitamin D intake, as compared with the lowest, correlated with a 50% lower risk of breast cancer.⁶⁴ Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin's lymphoma⁶⁵ and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.⁶⁶

The conundrum here is that since the kidneys tightly regulate the production of 1,25-dihydroxyvitamin D, serum levels do not rise in response to increased exposure to sunlight or increased intake of vitamin D.¹⁻³ Furthermore, in a vitamin D-insufficient state, 1,25-dihydroxyvitamin D levels are often normal or even elevated.^{1,3,6,7} The likely explanation is that colon, prostate, breast, and other tissues express 25-hydroxyvitamin D-1 α -hydroxylase and produce 1,25-dihydroxyvitamin D locally to control genes that help to prevent cancer by keeping cellular proliferation and differentiation in check.^{1-3,47,56,58} It has been suggested that if a cell becomes malignant, 1,25-dihydroxyvitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive.^{2,3,7,67} Once 1,25-dihydroxyvitamin D completes these tasks, it initiates its own destruction by stimulating the CYP24 gene to produce the inactive calcitric acid. This guarantees that 1,25-dihydroxyvitamin D does not enter the circulation to influence calcium metabolism (Fig. 1).¹⁻⁴ This is a plausible explanation for why increased sun exposure and higher circulating levels of 25-hydroxyvitamin D are associated with a decreased risk of deadly cancers.⁵⁶⁻⁶⁵

AUTOIMMUNE DISEASES, OSTEOARTHRITIS, AND DIABETES

Living at higher latitudes increases the risk of type 1 diabetes, multiple sclerosis, and Crohn's disease.^{68,69} Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%.^{69,70} Among white men and women, the risk of multiple sclerosis decreased by 41% for every increase of 20 ng per milliliter in 25-hydroxyvitamin D above approximately 24 ng per milliliter (60 nmol per liter) (odds ratio, 0.59; 95% CI, 0.36 to 0.97; $P=0.04$).⁷¹ Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing multi-

ple sclerosis.⁷² Similar observations have been made for rheumatoid arthritis⁷³ and osteoarthritis.⁷⁴

Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.⁵³ For 10,366 children in Finland who were given 2000 IU of vitamin D₃ per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80% (relative risk, 0.22; 95% CI, 0.05 to 0.89).⁷⁵ Among children with vitamin D deficiency the risk was increased by approximately 200% (relative risk, 3.0; 95% CI, 1.0 to 9.0). In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.⁵³ Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.⁷⁶

CARDIOVASCULAR DISEASE

Living at higher latitudes increases the risk of hypertension and cardiovascular disease.^{54,77} In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mm Hg).⁷⁸ Vitamin D deficiency is associated with congestive heart failure⁵⁴ and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.^{54,79}

VITAMIN D DEFICIENCY AND OTHER DISORDERS

SCHIZOPHRENIA AND DEPRESSION

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression.^{80,81} Maintaining vitamin D sufficiency in utero and during early life, to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.⁸²

LUNG FUNCTION AND WHEEZING ILLNESSES

Men and women with a 25-hydroxyvitamin D level above 35 ng per milliliter (87 nmol per liter) had

Table 2. Causes of Vitamin D Deficiency.*

Cause	Effect
Reduced skin synthesis	
Sunscreen use — absorption of UVB radiation by sunscreen ^{1-3,7,85}	Reduces vitamin D ₃ synthesis — SPF 8 by 92.5%, SPF 15 by 99%
Skin pigment — absorption of UVB radiation by melanin ^{1-3,7,85}	Reduces vitamin D ₃ synthesis by as much as 99%
Aging — reduction of 7-dehydrocholesterol in the skin ^{2,7,85}	Reduces vitamin D ₃ synthesis by about 75% in a 70-year-old
Season, latitude, and time of day — number of solar UVB photons reaching the earth depending on zenith angle of the sun (the more oblique the angle, the fewer UVB photons reach the earth) ^{1-3,85}	Above about 35 degrees north latitude (Atlanta), little or no vitamin D ₃ can be produced from November to February
Patients with skin grafts for burns — marked reduction of 7-dehydrocholesterol in the skin	Decreases the amount of vitamin D ₃ the skin can produce
Decreased bioavailability	
Malabsorption — reduction in fat absorption, resulting from cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, medications that reduce cholesterol absorption, and other causes ^{86,87}	Impairs the body's ability to absorb vitamin D
Obesity — sequestration of vitamin D in body fat†	Reduces availability of vitamin D
Increased catabolism	
Anticonvulsants, glucocorticoids, HAART (AIDS treatment), and antirejection medications — binding to the steroid and xenobiotic receptor or the pregnane X receptor ^{1-3,7,88}	Activates the destruction of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to inactive calcitroic acid
Breast-feeding	
Poor vitamin D content in human milk ^{1,33,89}	Increases infant risk of vitamin D deficiency when breast milk is sole source of nutrition
Decreased synthesis of 25-hydroxyvitamin D	
Liver failure	
Mild-to-moderate dysfunction	Causes malabsorption of vitamin D, but production of 25-hydroxyvitamin D is possible ^{2,3,6,7,90}
Dysfunction of 90% or more	Results in inability to make sufficient 25-hydroxyvitamin D
Increased urinary loss of 25-hydroxyvitamin D	
Nephrotic syndrome — loss of 25-hydroxyvitamin D bound to vitamin D-binding protein in urine	Results in substantial loss of 25-hydroxyvitamin D to urine ^{2,3,6,91}
Decreased synthesis of 1,25-dihydroxyvitamin D	
Chronic kidney disease	
Stages 2 and 3 (estimated glomerular filtration rate, 31 to 89 ml/min/1.73 m ²)	Causes decreased fractional excretion of phosphorus and decreased serum levels of 1,25-dihydroxyvitamin D
Hyperphosphatemia increases fibroblast growth factor 23, which decreases 25-hydroxyvitamin D-1 α -hydroxylase activity ^{5,6,91-94}	
Stages 4 and 5 (estimated glomerular filtration rate <30 ml/min/1.73 m ²)	Causes hypocalcemia, secondary hyperparathyroidism, and renal bone disease
Inability to produce adequate amounts of 1,25-dihydroxyvitamin D ^{2,3,6,91-96}	

a 176-ml increase in the forced expiratory volume in 1 second.⁸³ Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses.⁸⁴

CAUSES OF VITAMIN D DEFICIENCY

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D and acquired and heritable disorders of

Table 2. (Continued.)

Cause	Effect
Heritable disorders — rickets	
Pseudovitamin D deficiency rickets (vitamin D-dependent rickets type 1) — mutation of the renal 25-hydroxyvitamin D-1 α -hydroxylase gene (<i>CYP27B1</i>) ^{1,3,97}	Causes reduced or no renal synthesis of 1,25-dihydroxyvitamin D
Vitamin D-resistant rickets (vitamin D-dependent rickets type 2) — mutation of the vitamin D receptor gene ^{1,3}	Causes partial or complete resistance to 1,25-dihydroxyvitamin D action, resulting in elevated levels of 1,25-dihydroxyvitamin D
Vitamin D-dependent rickets type 3 — overproduction of hormone-responsive-element binding proteins ⁹⁸	Prevents the action of 1,25-dihydroxyvitamin D in transcription, causing target-cell resistance and elevated levels of 1,25-dihydroxyvitamin D
Autosomal dominant hypophosphatemic rickets — mutation of the gene for fibroblast growth factor 23, preventing or reducing its breakdown ^{1,3,5,6,92}	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1 α -hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
X-linked hypophosphatemic rickets — mutation of the <i>PHEX</i> gene, leading to elevated levels of fibroblast growth factor 23 and other phosphatonins ^{1,3,5,6,92}	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1 α -hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Acquired disorders	
Tumor-induced osteomalacia — tumor secretion of fibroblast growth factor 23 and possibly other phosphatonins ^{1,3,5,6,92,99}	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1 α -hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Primary hyperparathyroidism — increase in levels of parathyroid hormone, causing increased metabolism of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D ^{2,3,6}	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels that are high-normal or elevated
Granulomatous disorders, sarcoidosis, tuberculosis, and other conditions, including some lymphomas — conversion by macrophages of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D ¹⁰⁰	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels
Hyperthyroidism — enhanced metabolism of 25-hydroxyvitamin D	Reduces levels of 25-hydroxyvitamin D

* UVB denotes ultraviolet B, SPF sun protection factor, and HAART highly active antiretroviral therapy.

† There is an inverse relationship between the body-mass index and 25-hydroxyvitamin D levels.^{2,7,85}

vitamin D metabolism and responsiveness.^{2,3,6} Table 2 lists causes and effects of vitamin D deficiency.

VITAMIN D REQUIREMENTS AND TREATMENT STRATEGIES

CHILDREN AND ADULTS

Recommendations from the Institute of Medicine for adequate daily intake of vitamin D are 200 IU for children and adults up to 50 years of age, 400 IU for adults 51 to 70 years of age, and 600 IU for adults 71 years of age or older.¹⁰¹ However, most experts agree that without adequate sun exposure, children and adults require approximately 800 to 1000 IU per day.^{1-3,8,15,16,20,102,103} Children with vitamin D deficiency should be aggressively treated to prevent rickets (Table 3).^{1,28,105-107} Since vitamin D₂ is approximately 30% as effective as vitamin D₃ in maintaining serum 25-hydroxyvitamin

D levels,^{117,118} up to three times as much vitamin D₂ may be required to maintain sufficient levels. A cost-effective method of correcting vitamin D deficiency and maintaining adequate levels is to give patients a 50,000-IU capsule of vitamin D₂ once a week for 8 weeks, followed by 50,000 IU of vitamin D₂ every 2 to 4 weeks thereafter (Table 3).^{2,7,9} Alternatively, either 1000 IU of vitamin D₃ per day (available in most pharmacies) or 3000 IU of vitamin D₂ per day is effective.^{2,7,102,103} Strategies such as having patients take 100,000 IU of vitamin D₃ once every 3 months have been shown to be effective in maintaining 25-hydroxyvitamin D levels at 20 ng per milliliter or higher and are also effective in reducing the risk of fracture.¹¹⁹

BREAST-FED INFANTS AND CHILDREN

Human milk contains little vitamin D (approximately 20 IU per liter), and women who are vitamin D-deficient provide even less to their breast-

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation ^{28,33,89,104} — up to 1 yr	400 IU of vitamin D ₃ /day, ^{1,28,104} sensible sun exposure, ¹ 1000–2000 IU of vitamin D ₃ /day is safe, ^{1,2,27,75} maintenance dose is 400–1000 IU of vitamin D ₃ /day ^{1,2,104}	200,000 IU of vitamin D ₃ every 3 mo, ^{1,105} 600,000 IU of vitamin D intramuscularly, repeat in 12 wk ¹⁰⁶ ; 1000–2000 IU of vitamin D ₂ or vitamin D ₃ /day ^{1,107} with calcium supplementation
Inadequate sun exposure ^{24,29–31,108} or supplementation, ^{1,28,104–107} dark skin ²³ — 1 through 18 yr	400–1000 IU vitamin D ₃ /day, ^{1,104,107} sensible sun exposure, 1000–2000 IU of vitamin D ₃ /day ^{1,108} is safe, ^{1,27,75,104,107} maintenance dose is 400–1000 IU of vitamin D ₃ /day ^{1,75}	50,000 IU of vitamin D ₂ every wk for 8 wk ^{1,94}
Adults		
Inadequate sun exposure ^{7,15} or supplementation, ^{7,20} decreased 7-dehydrocholesterol in skin because of aging (over 50 yr) ⁷	800–1000 IU of vitamin D ₃ /day, ^{1–3,8,16,21,42} 50,000 IU of vitamin D ₂ every 2 wk or every mo, ^{7,9} sensible sun exposure ^{7,15,109,110} or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp), ^{111–114} up to 10,000 IU of vitamin D ₃ /day is safe for 5 mo, ²⁷ maintenance dose is 50,000 IU every 2 wk or every mo ^{7,94}	50,000 IU of vitamin D ₂ every wk for 8 weeks ⁹ ; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization, ³³ inadequate sun exposure ^{33,89} or supplementation ^{33,89})	1000–2000 IU of vitamin D ₃ /day, ^{33,89} 50,000 IU of vitamin D ₂ every 2 wk, up to 4000 IU of vitamin D ₃ /day is safe for 5 mo, ^{33,89} maintenance dose is 50,000 IU of vitamin D ₂ every 2 or 4 wk ⁹⁴	50,000 IU vitamin D ₂ every wk for 8 wk ¹¹⁵ ; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Malabsorption syndromes (malabsorption of vitamin D, ^{2,3,86,87} inadequate sun exposure ^{2,3,6,7} or supplementation ^{2,3,6,7})	Adequate exposure to sun or ultraviolet radiation, ^{7,113} 50,000 IU of vitamin D ₂ every day, every other day, or every wk,† up to 10,000 IU of vitamin D ₃ /day is safe for 5 mo, ²⁷ maintenance dose is 50,000 IU of vitamin D ₂ every wk‡	UVB irradiation (tanning bed or portable UVB device, e.g., portable Sperti lamp), ^{111–114} 50,000 IU of vitamin D ₂ every day or every other day‡
Drugs that activate steroid and xenobiotic receptor, ⁸⁸ and drugs used in transplantation ¹¹⁶	50,000 IU of vitamin D ₂ every other day or every week, maintenance dose is 50,000 IU of vitamin D ₂ every 1, 2, or 4 wk‡	50,000 IU of vitamin D ₂ every 2 wk for 8–10 wk, or every wk if 25-hydroxyvitamin D <30 ng/ml‡
Obesity ^{2,7}	1000–2000 IU of vitamin D ₃ /day, 50,000 IU of vitamin D ₂ every 1 or 2 wk, maintenance dose is 50,000 IU of vitamin D ₂ every 1, 2, or 4 wk‡	50,000 IU of vitamin D ₂ every wk for 8–12 wk; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Nephrotic syndrome ^{2,3,6,7,91–94}	1000–2000 IU of vitamin D ₃ /day, 50,000 IU of vitamin D ₂ once or twice/wk, ^{2,94} maintenance dose is 50,000 IU of vitamin D ₂ every 2 or 4 wk ²⁴	50,000 IU of vitamin D ₂ twice/wk for 8–12 wk ^{2,94} ; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Chronic kidney disease§		
Stages 2 and 3	Control serum phosphate, ⁶ 1000 IU of vitamin D ₃ /day, 50,000 IU of vitamin D ₂ every 2 wk, ^{91,94} maintenance dose is 50,000 IU of vitamin D ₂ every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained‡	50,000 IU of vitamin D ₂ once/wk for 8 wk ^{91,94} ; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Stages 4 and 5	1000 IU of vitamin D ₃ /day, ⁵¹ 50,000 IU of vitamin D ₂ every 2 wk, need to treat with 1,25-dihydroxyvitamin D ₃ or active analogue‡	0.25–1.0 µg of 1,25-dihydroxyvitamin D ₃ (calcitriol) ^{2,6,91,93,94} by mouth twice a day or one of the following: 1–2 µg of paricalcitol IV every 3 days, ^{6,91,93,94} 0.04–0.1 µg/kg IV every other day initially and can increase to 0.24 µg/kg, 2–4 µg by mouth three times/wk, ^{6,91,93,94} or doxercalciferol ^{6,91,93,94} 10–20 µg by mouth three times/wk or 2–6 µg IV three times/wk

Table 3. (Continued.)

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Adults		
Primary or tertiary hyperparathyroidism	800–1000 IU of vitamin D ₃ /day, 50,000 IU of vitamin D ₂ every 2 wk (serum calcium levels will not increase), ¹¹⁵ maintenance dose is 50,000 IU of vitamin D ₂ every 2 or 4 wk‡	50,000 IU of vitamin D ₂ once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml
Granulomatous disorders and some lymphomas	400 IU of vitamin D ₃ /day, maintenance dose is 50,000 IU of vitamin D ₂ /mo‡	50,000 IU vitamin D ₂ once a wk for 4 wk or every 2 to 4 wk, need to keep 25-hydroxyvitamin D between 20 and 30 ng/ml (level above 30 ng/ml can result in hypercalciuria and hypercalcemia)‡

* These recommendations are based on published literature and the author's personal experience. IV denotes intravenously. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.

† For the specific mechanism of deficiency, see Table 2.

‡ The goal is to achieve concentrations of 25-hydroxyvitamin D at about 30 to 60 ng per milliliter. Physicians should use these guidelines in combination with their clinical judgment according to the circumstances.

§ In stages 2 and 3 of chronic kidney disease, the estimated glomerular filtration rate is 31 to 89 ml per minute per 1.73 m²; in stages 4 and 5, the estimated rate is <30 ml per minute per 1.73 m².

fed infants.^{33,89} Lactating women given 4000 IU of vitamin D₃ per day not only had an increase in the level of 25-hydroxyvitamin D to more than 30 ng per milliliter but were also able to transfer enough vitamin D₃ into their milk to satisfy an infant's requirement.⁸⁹

In Canada, to prevent vitamin D deficiency, current guidelines recommend that all infants and children receive 400 IU of vitamin D₃ per day (Table 3).¹⁰⁴

PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with any stage of chronic kidney disease, 25-hydroxyvitamin D should be measured annually, and the level should be maintained at 30 ng per milliliter or higher, as recommended in the Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation.^{6,91,93,94} It is a misconception to assume that patients taking an active vitamin D analogue have sufficient vitamin D; many do not. Levels of 25-hydroxyvitamin D are inversely associated with parathyroid hormone levels, regardless of the degree of chronic renal failure.^{2,6,93–96} Parathyroid glands convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which directly inhibits parathyroid hormone expression.^{6,93–96,120} Patients with stage 4 or 5 chronic kidney disease and an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m² of body-surface area, as well as those requiring dialysis, are unable to make enough 1,25-dihydroxyvitamin D and need to take 1,25-dihydroxyvitamin D₃ or one of its less calcemic analogues to maintain calcium metabolism and to decrease parathyroid hormone levels and the risk of renal bone disease (Table 3).^{6,91,93,94}

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MALABSORPTION AND MEDICATION

Patients with mild or moderate hepatic failure or intestinal fat-malabsorption syndromes, as well as patients who are taking anticonvulsant medications, glucocorticoids, or other drugs that activate steroid and xenobiotic receptor, require higher doses of vitamin D (Table 3).^{7,88} Exposure to sunlight or ultraviolet B radiation from a tanning bed or other ultraviolet B-emitting device is also effective.^{7,113,115}

SUNLIGHT AND ARTIFICIAL ULTRAVIOLET B RADIATION

Sensible sun exposure can provide an adequate amount of vitamin D₃, which is stored in body fat and released during the winter, when vitamin D₃ cannot be produced.^{7,15,85,108–110} Exposure of arms and legs for 5 to 30 minutes (depending on time of day, season, latitude, and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week is often adequate.^{2,7,108–110} Exposure to one minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of approximately 20,000 IU of vitamin D₃.^{1,2,7,85} The skin has a great capacity to make vitamin D₃, even in the elderly, to reduce the risk of fracture.^{109–111} Most tanning beds

emit 2 to 6% ultraviolet B radiation and are a recommended source of vitamin D₃ when used in moderation.^{111-113,115} Tanners had robust levels of 25-hydroxyvitamin D (approximately 45 ng per milliliter [112 nmol per liter]) at the end of the winter and higher bone density as compared with nontanners (with levels of approximately 18 ng per milliliter [45 nmol per liter]).¹¹² For patients with fat malabsorption, exposure to a tanning bed for 30 to 50% of the time recommended for tanning (with sunscreen on the face) is an excellent means of treating and preventing vitamin D deficiency (Table 3).¹¹³ This reduces the risk of skin cancers associated with ultraviolet B radiation.

VITAMIN D INTOXICATION

Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia.^{1-3,27,121,122} Doses of 10,000 IU of vitamin D₃ per day for up to 5 months, however, do not cause toxicity.²⁷ Patients with chronic granulomatous disorders are more sensitive to serum 25-hydroxyvitamin D levels above 30 ng per milliliter because of macrophage production of 1,25-dihydroxyvitamin D, which causes hypercalciuria and hypercalcemia.^{1-3,100} In these patients, however, 25-hydroxyvitamin D levels need to be maintained at approximately 20 to 30 ng per milliliter to prevent vitamin D deficiency and secondary hyperparathyroidism (Table 3).^{1-3,100}

CONCLUSIONS

Undiagnosed vitamin D deficiency is not uncommon,^{1-3,6-20,123} and 25-hydroxyvitamin D is the barometer for vitamin D status. Serum 25-hydroxyvitamin D is not only a predictor of bone health⁸ but is also an independent predictor of risk for cancer and other chronic diseases.^{8,54,59-64,71-75,83-85}

The report that postmenopausal women who increased their vitamin D intake by 1100 IU of vitamin D₃ reduced their relative risk of cancer by 60 to 77% is a compelling reason to be vitamin D-sufficient.¹²⁴ Most commercial assays for 25-hydroxyvitamin D are good for detecting vitamin D deficiency. Radioimmunoassays measure total 25-hydroxyvitamin D, which includes levels of both 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃. Some commercial laboratories measure 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ with liquid chromatography and tandem mass spectroscopy and report the values separately. As long as the combined total is 30 ng per milliliter or more, the patient has sufficient vitamin D.^{7,14,27} The 1,25-dihydroxyvitamin D assay should never be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism. Because the 25-hydroxyvitamin D assay is costly and may not always be available, providing children and adults with approximately at least 800 IU of vitamin D₃ per day or its equivalent should guarantee vitamin D sufficiency unless there are mitigating circumstances (Table 2).

Much evidence suggests that the recommended adequate intakes are actually inadequate and need to be increased to at least 800 IU of vitamin D₃ per day. Unless a person eats oily fish frequently, it is very difficult to obtain that much vitamin D₃ on a daily basis from dietary sources. Excessive exposure to sunlight, especially sunlight that causes sunburn, will increase the risk of skin cancer.^{125,126} Thus, sensible sun exposure (or ultraviolet B irradiation) and the use of supplements are needed to fulfill the body's vitamin D requirement.

Supported in part by grants from the National Institutes of Health (M01RR00533 and AR36963) and the UV Foundation.

Dr. Holick reports receiving honoraria from Merck, Eli Lilly, and Procter & Gamble and consulting fees from Quest Diagnostics, Amgen, Novartis, and Procter & Gamble. No other potential conflict of interest relevant to this article was reported.

I thank Dr. Farhad Chimeh for his helpful review of an earlier version of this manuscript and Donna Gendron and Lorrie MacKay for their secretarial assistance.

REFERENCES

- Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006; 116:2062-72.
- Holick MF, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 6th ed. Washington, DC: American Society for Bone and Mineral Research, 2006:129-37.
- Bouillon R. Vitamin D: from photosynthesis, metabolism, and action to clinical applications. In: DeGroot LJ, Jameson JL, eds. *Endocrinology*. Philadelphia: W.B. Saunders, 2001:1009-28.
- DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004;80:Suppl:1689S-1696S.
- Hruska KA. Hyperphosphatemia and hypophosphatemia. In: Favus MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 6th

- ed. Washington, DC: American Society for Bone and Mineral Research, 2006:233-42.
6. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005;289:F8-F28.
7. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006;81:353-73.
8. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18-28. [Erratum, *Am J Clin Nutr* 2006;84:1253.]
9. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351:805-6.
10. Thomas KK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998;338:777-83.
11. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997;7:439-43.
12. Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005;90:3215-24.
13. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003;22:142-6.
14. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005;16:713-6.
15. Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med* 2000;247:260-8.
16. Boonen S, Bischoff-Ferrari HA, Cooper C, et al. Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. *Calcif Tissue Int* 2006;78:257-70.
17. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001;22:477-501.
18. Bakhtiyarova S, Lesnyak O, Kyznesova N, Blankenstein MA, Lips P. Vitamin D status among patients with hip fracture and elderly control subjects in Yekaterinburg, Russia. *Osteoporos Int* 2006;17:441-6.
19. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med* 1992;93:69-77.
20. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res* 2004;19:370-8.
21. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D₃ and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637-42.
22. Lips P, Hosking D, Lippuner K, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med* 2006;260:245-54.
23. Gordon CM, DePeters KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med* 2004;158:531-7.
24. Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF. Adolescent girls in Maine at risk for vitamin D insufficiency. *J Am Diet Assoc* 2005;105:971-4.
25. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr* 2002;76:187-92.
26. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 2002;112:659-62.
27. Vieth R. Why the optimal requirement for vitamin D₃ is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol* 2004;89:90:575-9.
28. Pettifor JM. Vitamin D deficiency and nutritional rickets in children in vitamin D. In: Feldman D, Pike JW, Glorieux FH, eds. *Vitamin D*. 2nd ed. Boston: Elsevier Academic Press, 2005:1065-84.
29. Sedrani SH. Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. *Ann Nutr Metab* 1984;28:181-5.
30. Marwaha RK, Tandon N, Reddy D, et al. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* 2005;82:477-82.
31. El-Hajj Fuleihan G, Nabulsi M, Choucair M, et al. Hypovitaminosis D in healthy schoolchildren. *Pediatrics* 2001;107:E53.
32. McGrath JJ, Kimlin MG, Saha S, Eyles DW, Parisi AV. Vitamin D insufficiency in south-east Queensland. *Med J Aust* 2001;174:150-1.
33. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr* 2004;79:717-26.
34. Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clin Pediatr (Phila)* 2007;46:42-4.
35. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr* 2007;137:447-52.
36. Cooper C, Javaid K, Westlake S, Harvey N, Dennison E. Developmental origins of osteoporotic fracture: the role of maternal vitamin D insufficiency. *J Nutr* 2005;135:2728S-2734S.
37. Sahota O, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int* 2006;17:1013-21. [Erratum, *Osteoporos Int* 2006;17:1825-6.]
38. Aaron JE, Gallagher JC, Anderson J, et al. Frequency of osteomalacia and osteoporosis in fractures of the proximal femur. *Lancet* 1974;1:229-33.
39. Gloth FM III, Lindsay JM, Zelesnick LB, Greenough WB III. Can vitamin D deficiency produce an unusual pain syndrome? *Arch Intern Med* 1991;151:1662-4.
40. Malabanan AO, Turner AK, Holick MF. Severe generalized bone pain and osteoporosis in a premenopausal black female: effect of vitamin D replacement. *J Clin Densitometr* 1998;1:201-4.
41. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003;78:1463-70.
42. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337:670-6.
43. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83. [Erratum, *N Engl J Med* 2006;354:1102.]
44. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D₃ and calcium for secondary prevention of low trauma fractures in elderly people (Randomised Evaluation of Calcium Or Vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005;365:1621-8.
45. Porthouse J, Cockayne S, King C, et al. Randomized controlled trial of supplementation with calcium and cholecalciferol (vitamin D₃) for prevention of fractures in primary care. *BMJ* 2005;330:1003-6.
46. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 2007;55:234-9.
47. Nagpal S, Na S, Rathnachalam R. Nonskeletal actions of vitamin D receptor ligands. *Endocr Rev* 2005;26:662-87.
48. Holick MF. Clinical efficacy of 1,25-dihydroxyvitamin D₃ and its analogues in the treatment of psoriasis. *Retinoids* 1998;14:12-7.
49. Kragballe K, Barnes L, Hamberg KJ, et al. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. *Br J Dermatol* 1998;139:649-54.

50. Penna G, Roncari A, Armuchastegui S, et al. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4⁺Foxp3⁺ regulatory T cells by 1,25-dihydroxyvitamin D₃. *Blood* 2005;106:3490-7.
51. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;311:1770-3.
52. Li YC. Vitamin D regulation of the renin-angiotensin system. *J Cell Biochem* 2003;88:327-31.
53. Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. *Am J Clin Nutr* 2004;79:820-5.
54. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006;92:39-48.
55. Apperly FL. The relation of solar radiation to cancer mortality in North America. *Cancer Res* 1941;1:191-5.
56. Gorham ED, Garland CF, Garland FC, et al. Vitamin D and prevention of colorectal cancer. *J Steroid Biochem Mol Biol* 2005;97:179-94.
57. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality: evidence for a protective effect of ultraviolet radiation. *Cancer* 1992;70:2861-9.
58. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 2002;94:1867-75.
59. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* 2006;98:451-9.
60. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* 2000;11:847-52.
61. Feskanich D, Ma J, Fuchs CS, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2004;13:1502-8.
62. Holick MF. Calcium plus vitamin D and the risk of colorectal cancer. *N Engl J Med* 2006;354:2287-8.
63. Luscombe CJ, Fryer AA, French ME, et al. Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer. *Lancet* 2001;358:641-2.
64. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *Am J Public Health* 2006;96:252-61.
65. Chang ET, Smedby KE, Hjalgrim H, et al. Family history of hematopoietic malignancy and risk of lymphoma. *J Natl Cancer Inst* 2005;97:1466-74.
66. Berwick M, Armstrong BK, Ben-Porat L, et al. Sun exposure and mortality from melanoma. *J Natl Cancer Inst* 2005;97:195-9.
67. Mantell DJ, Owens PE, Bundred NJ, Mawer EB, Canfield AE. 1 α ,25-dihydroxyvitamin D₃ inhibits angiogenesis in vitro and in vivo. *Circ Res* 2000;87:214-20.
68. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D₃, and the immune system. *Am J Clin Nutr* 2004;80:Suppl 6:1717S-1720S.
69. Ponsonby A-L, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. *Toxicology* 2002;181:182-71-8.
70. VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple sclerosis and vitamin D: an update. *Eur J Clin Nutr* 2004;58:1095-109.
71. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006;296:2832-8.
72. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;62:60-5.
73. Merlino LA, Curtis J, Mikuls TR, Cernan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum* 2004;50:72-7.
74. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med* 1996;125:353-9.
75. Hypponen E, Laara E, Reunanen A, Jarvelin M-R, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;358:1500-3.
76. Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006;29:650-6.
77. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 1997;30:150-6.
78. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet* 1998;352:709-10.
79. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Körfre R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol* 2003;41:105-12.
80. McGrath J, Selden JP, Chant D. Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration — data from Australia and the Netherlands. *Schizophr Res* 2002;54:199-212.
81. Gloth FM III, Alam W, Hollis B. Vitamin D vs. broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging* 1999;3:5-7.
82. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 α -hydroxylase in human brain. *J Chem Neuroanat* 2005;29:21-30.
83. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the Third National Health and Nutrition Examination Survey. *Chest* 2005;128:3792-8.
84. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 2007;85:788-95.
85. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004;79:362-71. [Erratum, *Am J Clin Nutr* 2004;79:890.]
86. Lo CW, Paris PW, Clemens TL, Nolan J, Holick MF. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. *Am J Clin Nutr* 1985;42:644-9.
87. Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab* 2005;90:1888-96.
88. Zhou C, Assem M, Tay JC, et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. *J Clin Invest* 2006;116:1703-12.
89. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr* 2004;80:Suppl 6:1752S-1758S.
90. Gascon-Barre M. The vitamin D 25-hydroxylase. In: Feldman D, Pike JW, Glorieux FH, eds. *Vitamin D*. 2nd ed. Boston: Elsevier Academic Press, 2005:47-68.
91. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42:Suppl 3:S1-S201.
92. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res* 2004;19:429-35.
93. Brown AJ. Therapeutic uses of vitamin D analogues. *Am J Kidney Dis* 2001;38:Suppl 5:S3-S19.
94. Holick MF. Vitamin D for health and in chronic kidney disease. *Semin Dial* 2005;18:266-75.
95. Ritter CS, Armbricht HJ, Slatopolsky E, Brown AJ. 25-Hydroxyvitamin D₃ suppresses PTH synthesis and secretion by bovine parathyroid cells. *Kidney Int* 2006;70:654-9. [Erratum, *Kidney Int* 2006;70:1190.]
96. Dusso AS, Sato T, Arcidiacono MV, et al. Pathogenic mechanisms for parathyroid hyperplasia. *Kidney Int Suppl* 2006;102:S8-S11.

97. Kitanaka S, Takeyama K, Murayama A, et al. Inactivating mutations in the human 25-hydroxyvitamin D₃ 1 α -hydroxylase gene in patients with pseudovitamin D-deficiency rickets. *N Engl J Med* 1998; 338:653-61.
98. Chen H, Hewison M, Hu B, Adams JS. Heterogeneous nuclear ribonucleoprotein (hnRNP) binding to hormone response elements: a cause of vitamin D resistance. *Proc Natl Acad Sci U S A* 2003;100:6109-14.
99. Ward LM, Rauch F, White KE, et al. Resolution of severe, adolescent-onset hypophosphatemic rickets following resection of an FGF-23-producing tumour of the distal ulna. *Bone* 2004;34:905-11.
100. Adams JS, Hewison M. Hypercalcaemia caused by granuloma-forming disorders. In: Favus, MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 6th ed. Washington, DC: American Society for Bone and Mineral Research, 2006:200-2.
101. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board, Institute of Medicine. Vitamin D. In: *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999:250-87.
102. Tangpricha V, Koutkia P, Rieke SM, Chen TC, Perez AA, Holick MF. Fortification of orange juice with vitamin D: a novel approach for enhancing vitamin D nutritional health. *Am J Clin Nutr* 2003; 77:1478-83.
103. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003;77:204-10. [Erratum, *Am J Clin Nutr* 2003;78:1047.]
104. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr* 2004;80:Suppl 6:1710S-1716S.
105. Shah BR, Finberg L. Single-dose therapy for nutritional vitamin D-deficiency rickets: a preferred method. *J Pediatr* 1994; 125:487-90.
106. Thacher TD, Fischer PR, Pettifor JM, et al. A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. *N Engl J Med* 1999;341:563-8.
107. Markestad T, Halvorsen S, Halvorsen KS, Aksnes L, Aarskog D. Plasma concentrations of vitamin D metabolites before and during treatment of vitamin D deficiency rickets in children. *Acta Paediatr Scand* 1984;73:225-31.
108. Jones G, Dwyer T. Bone mass in prepubertal children: gender differences and the role of physical activity and sunlight exposure. *J Clin Endocrinol Metab* 1998; 83:4274-9.
109. Reid IR, Gallagher DJA, Bosworth J. Prophylaxis against vitamin D deficiency in the elderly by regular sunlight exposure. *Age Ageing* 1986;15:35-40.
110. Sato Y, Iwamoto J, Kanoko T, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in hospitalized, elderly women with Alzheimer's disease: a randomized controlled trial. *J Bone Miner Res* 2005;20:1327-33.
111. Chel VGM, Ooms ME, Popp-Snijders C, et al. Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly. *J Bone Miner Res* 1998;13:1238-42.
112. Tangpricha V, Turner A, Spina C, Decastro S, Chen T, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. *Am J Clin Nutr* 2004;80:1645-9.
113. Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. *Gastroenterology* 2001;121:1485-8.
114. de Nijs RNJ, Jacobs JWJ, Algra A, Lems WF, Bijlsma JWJ. Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D₃ analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. *Osteoporos Int* 2004;15: 589-602.
115. Holick EA, Lu Z, Holick MT, Chen TC, Sheperd J, Holick MF. Production of previtamin D₃ by a mercury arc lamp and a hybrid incandescent/mercury arc lamp. In: Holick MF, ed. *Biologic effects of light 2001: proceedings of a symposium*. Boston: Kluwer Academic, 2002:205-12.
116. Grey A, Lucas J, Horne A, Gamble G, Davidson JS, Reid IR. Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. *J Clin Endocrinol Metab* 2005;90: 2122-6.
117. Armas LAG, Hollis BW, Heaney RP. Vitamin D₂ is much less effective than vitamin D₃ in humans. *J Clin Endocrinol Metab* 2004;89:5387-91.
118. Trang HM, Cole DEC, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D₃ increases serum 25-hydroxyvitamin D more efficiently than does vitamin D₂. *Am J Clin Nutr* 1998;68:854-8.
119. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D₃ (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326:469-75.
120. Correa P, Segersten U, Hellman P, Akerstrom G, Westin G. Increased 25-hydroxyvitamin D₃ 1 α -hydroxylase and reduced 25-hydroxyvitamin D₃ 24-hydroxylase expression in parathyroid tumors — new prospects for treatment of hyperparathyroidism with vitamin D. *J Clin Endocrinol Metab* 2002;87:5826-9.
121. Adams JS, Lee G. Gains in bone mineral density with resolution of vitamin D intoxication. *Ann Intern Med* 1997;127:203-6.
122. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. *N Engl J Med* 2001; 345:66-7.
123. Kreiter SR, Schwartz RP, Kirkman HN Jr, Charlton PA, Calikoglu AS, Davenport M. Nutritional rickets in African American breast-fed infants. *J Pediatr* 2000;137:153-7.
124. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-91.
125. Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol* 2003;120:1087-93.
126. Wolpowitz D, Gilchrist BA. The vitamin D questions: how much do you need and how should you get it? *J Am Acad Dermatol* 2006;54:301-17.

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The New York Times

July 20, 2004

I BEG TO DIFFER

A Dermatologist Who's Not Afraid to Sit on the Beach

By GINA KOLATA

Dr. A. Bernard Ackerman, a dermatologist, spends much of his time diagnosing the potentially deadly cancer melanoma and other skin diseases.

But when he returned from a recent trip to Israel, he was, well, deeply tanned. Burnished brown, in fact. Dr. Ackerman did not use sunscreen on his trip. He did not give any thought to the hundreds of moles that speckle his body. He did not even put a hat on his bald head.

Other dermatologists may worry about getting melanoma from exposure to ultraviolet rays. But Dr. Ackerman, 67, a renowned expert in the field and the emeritus director of the Ackerman Academy of Dermatopathology in New York, said the link between melanoma and sun exposure was "not proven." He has scrutinized, one by one, the widely held precepts about melanoma and the sun, and found the evidence wanting. "The field is just replete with nonsense," he said. For example, it is commonly assumed that painful or blistering sunburns early in life set the stage for the skin cancer later on. But while some studies show a small association, Dr. Ackerman says, others show none. And even studies that do show an effect disagree on when the danger period for sunburns is supposed to be.

Taken as a whole, Dr. Ackerman argues, the research is inconsistent and fails to make the case. Common wisdom also has it that sunscreens protect against melanoma. But Dr. Ackerman points to a recent editorial in the journal *Archives of Dermatology* concluding that there was no evidence to support that idea. Finally, many people assert that the more intense a person's sun exposure, the greater the risk of melanoma. For example, Dr. Darrell S. Rigel, a New York dermatologist, points out that the incidence of melanoma increases as distance to the equator decreases. Dr. Rigel, a past president of the American Academy of Dermatology and the lead editor of "Cancer of the Skin," a major textbook in the field, cites this as a compelling reason to conclude that sun exposure causes the skin cancer.

But it is not compelling to Dr. Ackerman. Epidemiological data on melanoma, he says, are imprecise and inaccurate. In searching for the causes of other cancers, he argues, epidemiological data have led researchers astray, and by their nature they cannot demonstrate cause and effect. Stay out of the sun, Dr. Ackerman advises, but do it to avoid premature aging of the skin. If you are very fair, avoiding sunlight will also help prevent squamous cell carcinoma, a less dangerous cancer. But it would be a mistake, he says, to assume that avoiding sunlight or using sunscreens will offer protection from melanoma.

Dr. Ackerman has been enamored of the skin and its diseases since his earliest days as a resident at Columbia. Studying dermatology, to him, was like taking courses in art history. "If you know a

certain artist you can recognize him again," he said. "So it is with lesions in the skin. A lesion is like a painting or a piece of sculpture." He has spent most of his career in academia and has published 625 research papers. His list of honors and awards includes this year's the Master Award, given to one person a year by the American Academy of Dermatology.

In 1999 he started his own academy, supported by AmeriPath, a company that owns pathology laboratories. "I had nothing to sell - I was always in university life," Dr. Ackerman said. "If you'll excuse the expression and not think I'm a tart, they bought me." His academy, he says, is now the world's largest training center for dermatopathology. Dr. Ackerman, who is paid a flat salary, and his six associates examine more than 100,000 specimens and have done more than 4,000 consultations each year. Dr. Ackerman continues to teach and write, and also to ask for data and question his field's conventional wisdom. Challenging the link between sun and melanoma is part of this pattern.

Dr. Ackerman even questions whether the "epidemic" of melanoma proclaimed by many dermatologists exists. The definition of the cancer, he says, has changed over time, leading doctors to diagnose, remove and cure cancerous growths that once would not have been called melanoma. "The criteria today, clinically and histopathologically, are diametrically different from those 30 years ago," he said. In medical school, he continued, "we were taught that melanoma is a big, black, fungating tumor that kills. Who would have believed then that you can recognize melanoma for what it is when it is small and flat and the size of the fingernail on your pinky? You would have said they were insane."

Anyone who argues that sun exposure causes melanoma, Dr. Ackerman says, needs to explain why blacks and Asians get melanoma almost exclusively on skin that is not exposed to sunlight: the palms, soles, nails and mucous membranes. Even in whites, the most common melanoma sites - the leg in women, the trunk in men - are hardly the most sun-exposed body parts. It is not a popular argument. Dr. Rigel, reached by telephone in Hawaii, where he was vacationing, said it was perverse of Dr. Ackerman to pick the data apart. Melanoma, Dr. Rigel said, can occur "where the sun doesn't shine." But that is because sunlight suppresses immune cells in the skin's surface that ordinarily hold cancer at bay, he said. He himself stays pale, even in Hawaii, that land of intense sunlight. "I'm a dermatologist," he explained.

Dr. Ackerman does not buy the immune-system argument. It is a hypothesis to support the hypothesis that sun exposure causes melanoma, he says. But it is not evidence. Of course, Dr. Ackerman adds, he could be wrong. "If the evidence were compelling, I'd be the first to capitulate," he said. "I'd say: 'I tip my hat to you. Well done.' "

From: Overstreet, John [joverstreet@theita.com]
Sent: Friday, February 06, 2009 12:16 PM
To: Chris J. Gallus
Subject: FW: Canadians also dubbed Feb Vit D Deficiency Month apparently

Take the word of a Montana doctor....

Vitamin D deficiency increasingly an issue

<http://www.greatfallstribune.com/article/20090203/LIFESTYLE/902030307>

I have never been accused of being a prophet. Indeed, were it so, that would be a hard road. Prophets of old were beaten, spat upon, stoned and forced outside society. Of course, false prophets probably deserved it. Jesus was said to have remarked, as quoted by Christian scripture, that a man cannot be a prophet in his hometown.

Still, I became excited, and wrote about the ascendancy of vitamin D in the medical literature in this column on June 27, 2007.

In an article entitled "Vitamin D for Cancer: Look for a future emphasis of this therapy," I wrote of our need, as humans, to receive direct exposure to sunlight. By this process, the major storage form of vitamin D (Vit D2) is converted by UV radiation into Vit D3. D3 then passes through the liver and is converted to 25 D3. This compound then passes through the kidneys and is converted to 1,25 D3 which is the active form of the vitamin.

As detailed in that article, indigenous peoples of equatorial climes probably receive adequate sunlight, however, those populations which have migrated away from the equator are at risk for vitamin D deficiency. Modern studies reveal that this means an increased risk of cancer. Yes, a simple vitamin is now associated with prevention of several types of cancer as well as depression.

Furthermore, investigators are just beginning to re-examine vitamin D and its impact on public health. Of course the further away from the equator one lives, the more at risk one is. It seems our Canadian friends have gotten the message. (See <http://tinyurl.com/bb37lf>.)

Not only have Canadians declared this month their national "Vitamin D Deficiency Month," but they have estimated that 97 percent of their population is vitamin D deficient. Canadians have decided to push vitamin D deficiency as a major public health problem. No wonder.

Canadians are so far north, and their weather is so cool, that these stalwart cold weather Canucks obviously do not get adequate sunlight. My question is, "Who does?"

Because most of us, especially those with fair skin, avoid sun exposure intentionally out of a well-informed fear of sun-induced skin cancer, the stigma of vitamin D deficiency is surely more widespread than just Canada.

As a primary practitioner, I have been giving serious attention to the diagnosis of hypo- vitaminosis D in most all of my patients for several years. Over the past few months, I have tested vitamin D levels in practically all of my patients during their yearly checkups. The lab is simple to order as an add-on to the

usual screening tests.

I do not know the total number of patients tested. I can, however, tell you that the number of patients with a vitamin D level in the normal range can be numbered on one hand, with a few digits to spare! Of course, my practice is in Montana, just two hours south of the Canadian border.

In a patient population such as this, perhaps just being in Montana (or Canada) is a sufficient positive test for needing vitamin D supplements. Still, doctors like numbers for their charts and it is handy to know a patient's level so that replacement efforts can be adjusted as necessary.

This brooks the issue: "What is an adequate level?" We may not know that answer yet. Meanwhile, back to prophecy.

As more resources are assigned to the investigation of vitamin D, and as more people in the general population take vitamin D, we will get an increasingly accurate picture of its importance in prevention of cancer and other major diseases.

As for me, personally, I will take my vitamin D tablet tonight, as always, hoping to personally accrue a healthy benefit. Needless to say, I recommend that you talk to your doctor soon about your need for vitamin D supplementation.

Dan Gold is a board-certified family physician who treats U.S. military veterans in Great Falls. E-mail him at thehealerscorner@mac.com.

washingtonpost.com

Some Seek Guidelines to Reflect Vitamin D's Benefits

By Rob Stein
Washington Post Staff Writer
Friday, July 4, 2008; A01

A flurry of recent research indicating that Vitamin D may have a dizzying array of health benefits has reignited an intense debate over whether federal guidelines for the "sunshine vitamin" are outdated, leaving millions unnecessarily vulnerable to cancer, heart disease, diabetes and other ailments.

The studies have produced evidence that low levels of Vitamin D make men more likely to have heart attacks, breast and colon cancer victims less likely to survive, kidney disease victims more likely to die, and children more likely to develop diabetes. Two other studies suggested that higher Vitamin D levels reduce the risk of dying prematurely from any cause.

In response to these and earlier findings, several medical societies are considering new recommendations for a minimum daily Vitamin D intake, the American Medical Association recently called for the government to update its guidelines, and federal officials are planning to launch that effort.

But many leading experts caution that it remains premature for people to start taking large doses of Vitamin D. While the new research is provocative, experts argue that the benefits remain far from proven. Vitamin D can be toxic at high doses, and some studies suggest it could increase the risk for some health problems, experts say. No one knows what consequences might emerge from exposing millions of people to megadoses of the vitamin for long periods.

"The data are intriguing and serve as, no pun intended, food for further fruitful research," said Mary Frances Picciano, at the Office of Dietary Supplements of the National Institutes of Health. "But beyond that, the data are just not solid enough to make any new recommendations. We have to be cautious."

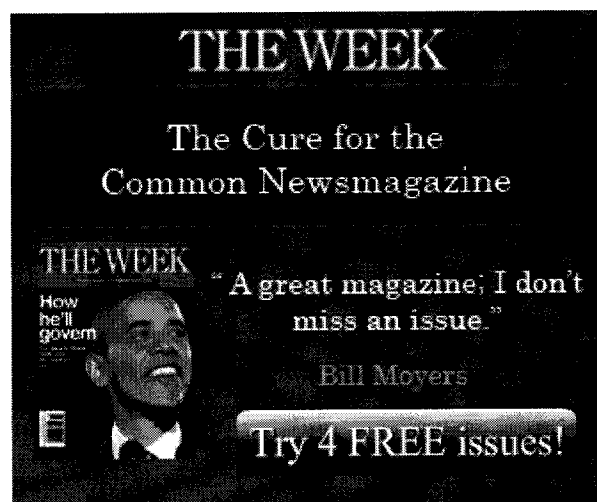
The current clash is the latest in a long, often unusually bitter debate. Some skeptics question whether funding by the tanning, milk and vitamin industries is biasing some advocates. Frustrated proponents accuse skeptics of clinging to outdated medical dogma.

"It feels kind of ridiculous working in this field sometimes," said Reinhold Vieth, a professor of nutritional sciences and pathobiology at the University of Toronto. "Every week, I get interviewed about the next important publication about Vitamin D. But this field remains mired in the muck."

Vieth is one of a small but vocal cadre of researchers pushing doctors and patients to stop waiting for new official guidelines. Physicians should routinely test their patients for Vitamin D deficiencies, and more people -- especially African Americans -- should take supplements and increase their exposure to the sun, they say.

"The bottom line is we now recognize that Vitamin D is important for health for both children and adults

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and may help prevent many serious chronic diseases," said Michael F. Holick, a professor of medicine, physiology and biophysics at Boston University.

Scientists have long known that Vitamin D is a vital nutrient the skin produces when hit by ultraviolet light from sunlight and other sources. The amount of Vitamin D produced varies, depending on where the person lives, skin pigment, age and other factors. African Americans and other dark-skinned people, and anyone living in northern latitudes, make far less than other groups.

With people spending more time indoors surfing the Web, watching television, working at desk jobs, and covering up and using sunblock when they do venture outdoors, the amount of Vitamin D that people create in their bodies has been falling. Milk and a few other foods are fortified with Vitamin D, and it occurs naturally in others, such as fatty fish, but most people get very little through their diets.

"Humans evolved in equatorial Africa wearing no clothes," said Robert P. Heaney, a leading Vitamin D researcher at Creighton University in Omaha. "Now we get much less direct sunlight, and so we don't make nearly as much Vitamin D."

A number of studies have found that deficiencies may be common, with perhaps half of adults and children having what some consider inadequate levels. Federal guidelines call for people to get 200 to 600 international units a day, depending on age and other factors. But those recommendations were last updated in 1997 and were aimed primarily at preventing bone diseases, such as rickets in children and osteoporosis in the elderly.

Since then, studies have indicated that Vitamin D offers a plethora of health benefits, possibly protecting against heart disease, many forms of cancer, immune system disorders such as multiple sclerosis and rheumatoid arthritis, infectious diseases such as tuberculosis and the flu, and perhaps mental illnesses including schizophrenia and depression.

"Vitamin D has a global effect on many systems," said Bruce Hollis, a professor of pediatrics, biochemistry and molecular biology at the Medical University of South Carolina.

The Canadian Cancer Society upped its recommendation to 1,000 units a day last year. Hollis and others believe Americans should routinely consume at least 2,000 international units a day.

"The first thing we'd see is a reduction by 80 percent in the incidence of Type 1 diabetes," said Cedric Garland, a professor of family and preventive medicine at the University of California at San Diego.

"The next thing we'd see is a reduction by about 75 percent of all invasive cancers combined, as well as similar reductions in colon cancer and breast cancer, and probably about a 25 percent reduction in ovarian cancer."

Holick urges people to take 1,000 international units a day along with a multivitamin with 400 international units, as well as exposing their arms and legs to the sun for about 15 minutes several times a week.

But others have reservations. Dermatologists worry that encouraging people to get unprotected sun exposure or use tanning salons may increase the rate of skin cancer.

"We're in the middle of a skin cancer epidemic," said C. William Hanke, president of the American Academy of Dermatology. "Tanning is risky and dangerous behavior. Ultraviolet light is classified as a carcinogen. We need to protect our skin."

Studies of other nutrients, such as Vitamin E, beta carotene and folate, have previously produced similarly promising findings only to turn out to be ineffective or even possibly dangerous, others say.

"We've gotten very excited in the past," said Alice Lichtenstein, a professor of nutrition at Tufts University who is a spokeswoman for the American Heart Association.

"It seems like an easy answer: We don't have to worry about losing weight or exercising. While I know the literature on Vitamin D is exploding, I think we have to be cautious until we've done the proper studies," Lichtenstein said.

Other skeptics go further, saying the Vitamin D already added to foods may be fueling increases in chronic diseases, such as diabetes and obesity.

"We call it a vitamin, but it's really a steroid," said Trevor G. Marshall, a molecular biologist at Murdoch University in Australia. "It's not something we should be playing with."

While still cautious, another skeptic, Leonard Lichtenfeld, deputy chief medical officer at the American Cancer Society, acknowledges that the evidence for Vitamin D is getting harder to ignore.

"I had a fair degree of skepticism. But now, while not a full-blown proponent, I believe it's definitely an area that needs more attention," Lichtenfeld said.

The National Academies' Institute of Medicine is negotiating with NIH and the Agriculture Department to make Vitamin D the first nutrient to be reassessed under a new system of evaluating nutritional requirements.

"Within the last four or five months, it's become a much more intensive dialogue," said Christine Taylor of the institute's Food and Nutrition Board. She cautioned, however, that the review, which could begin as early as the fall and take more than year, might leave the current recommendation unchanged.

"Some would argue there are significant new data about Vitamin D," Taylor said. "That doesn't mean that would change the requirement. But it implies a timely review is in order."

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Archive for Tuesday, June 10, 2008

Sunshine may be nature's disease fighter

Men lacking in vitamin D have more than double the normal risk of a heart attack, a study says, one of many suggesting the vitamin is crucial to good health.

By Thomas H. Maugh II
June 10, 2008

Medical researchers are homing in on a wonder drug that may significantly reduce the risk of heart disease, cancer, diabetes and many other diseases – sunshine.

A study released today found that men who are deficient in the so-called sunshine vitamin – vitamin D – have more than double the normal risk of suffering a heart attack.

Just last week, another study found that low levels of vitamin D increase the risk of diabetes, and a study last month linked deficiencies to an increased risk of dying from breast cancer.

The findings join a growing body of evidence indicating that an adequate level of the vitamin, which many people can get from 20 minutes in the sun, is crucial to maintaining good health.

Not every scientist agrees that vitamin D is so crucial to well-being, and there is controversy about what should be considered an adequate level of the compound in the blood. But sentiment is gradually shifting toward a higher intake.

"We don't have a cause and effect relationship here yet" proving that higher doses of vitamin D prevent such diseases, said biochemist Hector DeLuca of the University of Wisconsin, who was the first to demonstrate how the vitamin interacts with the endocrine system, which manages the body's hormonal balance.

But the links are so suggestive "that we have to pay attention to keeping blood levels up where they will protect," he said. Until the protective effect is proved, he added, "what's wrong with keeping an adequate level of vitamin D in the blood in case it is?"

Until recently, vitamin D was viewed primarily as a protective agent against diseases of the bone, such as osteomalacia (known as rickets in children) and osteoporosis. Current recommendations for the vitamin are based on preventing these disorders and call for a relatively small intake – a minimum of 400 international units, or IUs, per day, and perhaps twice that for the elderly, who may not get outdoors as often.

The vitamin is produced from natural precursors in the body by exposing skin to ultraviolet B in sunlight. Caucasian sunbathers can get 20,000 IUs in 20 minutes at noon in summer. But any further exposure simply damages skin.

Darker-skinned people need three to five times the exposure to produce the same amount. Sunblock interferes with production by screening out ultraviolet light.

The primary sources of vitamin D in the diet are milk, which is fortified to yield about 100 IUs per glass, and oily fishes, which have a high content. To have an adequate intake, most people must take supplements or spend more time in the sun – a recommendation that dermatologists generally oppose because of the risk of skin cancer.

Current guidelines call for blood levels of about 30 nanograms per milliliter. By that definition, perhaps 10% to 15% of white people in the U.S. and 50% of the black population is deficient in summer, with the levels rising in winter when there is less sunlight.

Many researchers now say that we should be striving for average blood levels of 50 to 60 nanograms per milliliter, at which level the bulk of the U.S. population would be considered deficient.

Most researchers in the field now take supplements of at least 1,500 IUs per day. Most recommend taking no more than 4,000 IUs because of potential toxicity.

Experts attribute the vitamin D deficiency, in part, to modern lifestyles, which have taken people off the farm and into offices and factories. Video games and computers have brought children indoors from the playing field, minimizing their exposure to sunlight. Fear of cancer and increasing use of sunblock may also have contributed.

In the new analysis, Dr. Edward Giovannucci of the Harvard School of Public Health and his colleagues studied 18,225 men enrolled in the Health Professionals Follow-Up Study, a subgroup of a much larger ongoing study. The men all submitted blood samples when they enrolled in the study, mostly in 1993 to 1995, and the samples were stored.

In 10 years of follow-up, the team identified 454 men who had a heart attack. They carefully matched these men with about 900 other study members who did not have an attack, then measured vitamin D levels at study entry.

They reported in the current issue of the Archives of Internal Medicine that men with blood levels below 15 nanograms per milliliter had 2 1/2 times the risk of having an attack or dying. When they controlled for all other possible factors, such as hypertension, obesity and high lipid levels, the risk was still twice as high as it was for the controls.

Men with levels between 15 and 29 nanograms per milliliter also had an increased risk. Unfortunately, Giovannucci said, there were not enough men in the group with levels above 35 nanograms per milliliter to determine whether higher levels are more protective.

The findings are "not out of left field," he said. Many epidemiological studies have found a higher rate of heart attacks at higher latitudes, lower altitudes and in winter – all of which correlates to decreased exposure to sunshine.

About 869,000 Americans die of heart disease each year, according to the American Heart Assn.

"They certainly have made the link between diabetes and cardiovascular disease," said Dr. Mason Weiss, a cardiologist at Centinela Hospital Medical Center in Inglewood, who was not involved in the study. "Now the research must be on what the mechanism is."

Giovannucci speculated that several mechanisms could be responsible. Previous studies have suggested, for example, that low vitamin D levels lead to a buildup of calcium in atherosclerotic plaques on the walls of arteries, increasing the risk of heart attacks.

It could also affect blood pressure, or even have a direct effect on functioning of heart muscles, making them more susceptible to arrhythmias.

"We obviously need to understand the mechanism better," he said. "But that requires randomized trials, which is a big undertaking."

Weiss joined the growing chorus of researchers calling for changes in federal guidelines to reflect the new data.

"The next time they review the daily requirements, they should look at all these articles," he said. Increasing the recommended intake of vitamin D "could have a significant health benefit" and would be a cost-effective change.

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